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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,000	03/16/2004	Thomas Nadackal Thomas	1996.01	2824

21901 7590 04/01/2010

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
04/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/802,000	THOMAS, THOMAS NADACKAL	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-34* is/are pending in the application.

4a) Of the above claim(s) *6,8-16,18,19 and 21-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 8-34 are pending in this application. Claims 6, 8-16, 18, 19 and 21-34 are withdrawn. Claims 1-5, 17 and 20 are rejected.

Applicants' arguments filed September 11, 2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 17 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing against NSAID gastric lesion and reducing the gastric ulceration resulting from administration of NSAIDs by pre or co-administering a monoamine oxidase inhibitor, it does not reasonably provide enablement for preventing gastrointestinal ulceration by administration of the plethora of agents in instant claim 2 some of which are actually not anti-inflammatory agents. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The term "prevention" is synonymous with a treatment having absolute success. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as gastrointestinal ulceration, the specification is viewed as lacking enablement.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

A. Breath of the Claims: The claims encompass prevention of gastrointestinal ulceration resulting from anti-inflammatory drugs which have potentially many different causes (Current evidence indicates that about 60% of peptic ulcers are caused by a bacterial infection (H. Pylori) that can usually be cured. Another 20% are caused by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen and another 20% have miscellaneous causes such as cigarettes or no clear cause (Medicinenet.com (U))). Each of these defects may or may not be addressed by the administration of the claimed compounds.

B. Nature of the Invention: Claim 1 is drawn to a method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs

and enhancing the beneficial effects of anti-inflammatory drugs. The nature of the invention is complex in that it encompasses the actual prevention of the development of a gastrointestinal ulcer such that the subject treated with an MAO inhibitor NSAID combination would not be afflicted with a gastrointestinal ulcer. However, the claims lack enablement due to the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

C. State of the Prior Art: The state of the art as presented by medicinenet.com states that 60% of peptic ulcers are caused by H pylori making the practice of the claimed invention unpredictable in terms of the role of an anti-inflammatory agent in causing the peptic ulcer, especially in that Applicant has indicated in instant claim 2 that

"helicobacter pylori inhibitors" are included in the list of agents that are anti-inflammatory drugs that cause the gastrointestinal ulceration effect.

D. The Level of One of Ordinary Skill: The relative skill of those in the art is generally that of a medical doctor.

E. Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual prevention and complete reversal of any and all gastrointestinal ulceration subject with the claimed anti-inflammatory agents makes practicing the claimed invention unpredictable in terms of prevention of gastrointestinal ulceration effects of anti-inflammatory drugs. Medicinenet (U) teach that 20% are caused by nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin and ibuprofen. Given the examples cited in the instant specification at table 3, the test compounds reduced gastric lesions, but clearly did not prevent gastric lesions.

F. Guidance of the Specification: The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually prevent gastrointestinal ulceration is minimal. All of the guidance provided by the specification is directed towards analgesic and anti-inflammatory activities of aspirin and indomethacin when combined with propargylamine or l-deprenyl. Additionally Table 3 indicates that there were no instances where a gastric lesion was prevented by the combination of indomethacin and aspirin when combined with l-deprenyl or propargylamine (page 25 of specification).

G. Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of gastric ulceration. None of the examples in Table 3 of the specification actually prevent gastric lesions. It is noted that there are examples where gastric lesions were reduced.

H. The amount of Experimentation Necessary: In order to practice claimed invention, one of skill in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of gastric ulceration. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of gastric ulceration, one of skill in the art would have to then either envision a modification of the MAO inhibitor/anti-inflammatory composition, dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification of prior art regarding prevention of gastric ulceration, the entire, unpredictable process would have to be repeated until successful. Because of the known unpredictability of the art and the broad spectrum of toxicities associated with anti-inflammatory drugs (as discussed supra) and in the absence of experimental

evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combination could be predictably used to prevent gastric ulceration caused by NSAIDs as inferred in the claims and contemplated by the specification.

It would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of gastric ulceration in a subject by administration of one of the claimed compounds.

Therefore, a method of preventing in a subject gastric ulceration administering the pharmaceutical composition of claim 1 is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai U.S. Patent No. 5,916,910 A

Lai teaches that NSAIDs cause gastrointestinal ulcers (column 1, lines 16-25) and teach treatment of ulcerogenic effects of NSAIDS such as COX-1 and COX-2 inhibitors comprising administering a conjugate of an NSAID and a nitric oxide

scavenger (column 2, line 60 to column 3, line 67) and MAO inhibitors such as selegiline (deprenyl), Parkinyl (column 15, lines 13-14), phenelzine sulfate, tranylcypromine sulfate (column 8, lines 19-28). Amide linkages are recited to covalently link the compounds (see column 22, lines 25-37 and claims 9 and 12).

Regarding the manner of linking of instant claim 20, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7, 17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glavin et al. (cite No. 4 IDS dates 3/16/04) and Lianping et al (U).

Glavin et al. teach there is an association between the occurrence of duodenal ulcers and dopamine deficiency in disorders such as Parkinson's disease. In addition, disorders characterized by excess dopamine activity, such as schizophrenia are rarely associated with duodenal pathology. It was shown that pretreatment with a selective MAO_b inhibitor, L-deprenyl, prevented duodenal ulcers in rats when they were administered the agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). (see page 379)

It does not teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs comprising administration of an MAO inhibitor.

Lianping et al. teach MAO inhibitors reduced restraint stress-induced gastric ulceration by inhibition of gastrin release (page 61) resulting in a protection of the gastric mucosa (page 63, column 1).

It does not teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs comprising administration of an MAO inhibitor.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to employ MAO inhibitors to prevent the toxic effects of anti-inflammatory agents motivated by the teaching of Glavin et al. that L-deprenyl, prevented duodenal ulcers in rats when they were administered the agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopamine depleting agent, known to cause gastric mucosal injury, thus demonstrating the protective utility of MAO inhibitors and by the teachings of Lianping et al. who demonstrates further inhibition of stress induced gastric ulceration by administration of MAO inhibitors to rats whereby release of gastrin is inhibited.

The protective gastrointestinal effect is disclosed in both references. It would have been obvious to employ the MAO inhibitors to provide a protective effect to the gastrointestinal mucosa when NSAIDs are administered.

One of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly

rejected and none are allowed.

Response to Arguments

In response to applicant's amendment to instant claim 1 removing the Word "toxic" and adding the word "ulceration", the rejection is withdrawn.

Regarding the 112 first paragraph rejection, all of Applicants remarks address treatment and reducing ulceration, not prevention. Applicant asserts that Glavin and Lianping studied only stress induced ulcers caused by cold exposure and Lianping expressly limited its teachings to determining protection via antisecretory effects of MAP-B inhibition. Applicant asserts that claim 1 is limited to NSAID induced gastric injury, however this does not appear to be the case. Claim 1 is limited to anti-inflammatory agents, that are selected from NSAIDs, steroids, acetaminophen, COX-3 inhibitors , 5-lipoxygenase inhibitors, leukotriene receptor antagonists, leukotriene A4 hydrolase inhibitors, angiotensin converting enzyme antagonists, antihistaminics, histamine 2 receptor antagonists, phosphodiesterase-4 antagonists, cytokine antagonists, CD44 antagonists, antineoplastic agents, 3-hydroxy-3-methylglutaryl coenzyme A inhibitors, statins, alpha blockers, beta blockers, estrogens, androgens, antiplatelet agents, antidepressants, Helicobacter pylori inhibitors, proton pump inhibitors, thiazolidinediones, dual-action compounds, combinations of these drugs with other agents, derivatives and metabolites of antiinflammatory agents. Further, the definition of anti-inflammatory toxicity is similarly broad in that it encompasses MAO inhibition, neuroprotection, endothelial protection, antiinflammatory action, antiplatelet

action, antiatherogenic action, inhibition of activation and migration of leukocytes, decreasing the levels inflammatory markers, antioxidant action, free radical scavenging, antiapoptotic action, reduction of hypoxia, reduction of oxidative stress, antagonism of cytotoxic actions of toxic agents, inhibition of tumor growth, vasodilation, increased blood flow, enhanced expression of antioxidant enzymes and growth factors, stimulation of constitutive nitric oxide synthase enzymes resulting in the enhanced production of nitric oxide, and inhibition of cytochrome P450 enzymes (instant claim 5). As such, all that is required of the MAO inhibitor is to inhibit monoamine oxidase to meet the claim.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

March 18, 2010